THE EVOLUTION AND ORGANIZATION OF THE UNIVERSITY CLINIC

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I

YOU are about to establish at the University of Oxford several new departments of the Medical School in connexion with the Radcliffe Infirmary. In these new departments the responsibility for the advancement of knowledge by research will equal the responsibility for the training of students in the practical pursuit of the profession of medicine. I wish first to congratulate the University on the acquisition of the great Nuffield benefaction which makes this departure possible, and I wish also to express my sense of the privilege it is to be present in Oxford during the inception of this great enterprise.

The times are propitious for such an innovation. Medical science has been moving with constantly increasing speed towards the ideals which you have set yourselves to achieve. Oxford has had its share in producing the famous men who have helped to make medicine scientific. It is only fitting that it should again establish a standard that the rest of Great Britain, and also the world, should come to emulate.

The establishment of clinics in medicine and surgery on a university basis would seem to involve three things:

1. The provision of laboratories in the clinic where there can be conducted scientific research equal in fundamental importance to that carried out by the general laboratories along with the training of students in scientific medicine and its methods.

2. Clinical professors who are qualified in at least one subject of medical research to be both leaders of their research associates and technical workers in one of the several laboratories attached to the clinic.
3. The power of the professor to command his time for the patients from whom the research problems are derived, for the laboratory in which those problems are investigated, and for the teaching of students in the science of their profession.

The key to the achievement of these conditions lies in the laboratories. I venture, therefore, at the outset to place before you in brief and incomplete fashion the history of the development of the laboratory where investigator and student meet and labour together, a development which within the last one hundred years has done more than anything else to give to medicine its scientific character.

Medicine has played a significant role in the development of the natural sciences, and laboratories existed and were fruitful long before the investigator-student laboratory was founded. Any one reading Sir Archibald Garrod's delightful essay on *The Debt of Science to Medicine*,[1] or Dr. William H. Welch's illuminating address on 'The Interdependence of Medicine and the Other Sciences of Nature',[2] cannot fail to realize the indispensable part which medicine has played in the history of science. If, therefore, to-day the sciences of biology, chemistry, and physics are playing increasing parts in the growth of the more

[1] Garrod, Archibald E., *The Debt of Science to Medicine, being the Harveian Oration*, Oxford, The Clarendon Press, 1924.

[2] Welch, W. H., *Science*, 1908, N.S. 27, 49.

particular medical sciences, this is only a just compensation for what medicine did for them in the past.

A student of the history of science[1] has said that the evolution of the modern laboratory still awaits its historian. The development of the chemical laboratory has been traced with some fullness, but the beginnings of other laboratories, the material circumstances under which the physicist, the chemist, the morphologist, and the physiologist of former generations worked remains still to be disclosed. 'This much', he said, 'we know: laboratories of sorts existed in very early times—in Alexandria under the Ptolemies, under the great Hohenstaufen Frederick II of Sicily, and of course from the sixteenth century on in increasing numbers after Vesalius published his immortal work on human anatomy in 1543. These earliest laboratories were places of instruction of students as well as for investigation. Private laboratories for investigation must also have existed from earliest times. Probably Aristotle had his laboratory. But methodical experimentation in the sciences of nature was definitely established by Galileo. There is no doubt that the learned societies which sprang up during the Renaissance period in Italy, Germany, England, and France greatly promoted the creation of the private laboratory—the laboratory, that is, for the scientifically-minded professional or amateur who carried out experiments with the aid of his personal assistants. But the laboratories which affected the development of university teaching were the investigator-student organizations, and they are just over one hundred years old.'

[1] Welch, W. H., *Johns Hopkins Hosp. Bull.*, 1896, 7, 19.

The investigator-student laboratory is an outgrowth and expansion of the private laboratory. These private laboratories flourished best in France at the beginning of the nineteenth century, but there was also a famous if modest one in Stockholm presided over by Berzelius. Hence it was to these centres that the ambitious youth from other countries, including Germany, repaired to receive instruction. German science, its medical science especially, was under the pernicious and sterilizing influence of the nature philosophy of Oken, Schilling, and Wieland, and while chemistry, a practical art chiefly, was perhaps less affected than medicine, yet the instruction was largely declamatory and authoritative even in that subject. There was a lack of opportunity and want of appreciation of experiment, the life blood of chemistry as of the other fundamental sciences, so that Liebig could write that 'from the professorial chair the pupils received an abundance of ingenious contemplations; but bodiless as they were, nothing could be made of them'.

The ambitious Liebig sought an outlet at Stockholm, as had also Mitscherlich, the discoverer of isomorphism, Rose, the analyst, and later Wöhler. But Liebig's lucky star soon diverted him to Paris, where extraordinary good fortune favoured him. In Paris there were, in the twenties of the nineteenth century, a few laboratories in which professor and assistant worked side by side. They were wretched affairs which Claude Bernard, who himself worked in a damp small cellar, called 'the tombs of scientific investigators'. As late as the middle fifties, when Pasteur had already solved the problem of lactic fermentation and had returned to the École Normale in Paris, he was assigned two bleak attics under the roof, without assistants—without even a laboratory attendant of any kind.[1] Admission even to these depressing places was difficult to obtain. Liebig, however, was admitted to the private laboratory of Gaultier de Claubry, where he completed a paper on explosives—on fulminating silver—which he presented before the Academy of Sciences. By chance, Alexander von Humboldt was present in the audience; his interest in the young chemist was excited and he arranged for him to meet Gay-Lussac, who opened his laboratory to the young man. Von Humboldt's assistance did not stop there, for it was on his recommendation that Liebig was afterwards appointed professor in the little university of Giessen.

It is usual to credit to Liebig the first teaching laboratory of modern times, the one he founded at Giessen in 1825; and romance has surrounded this laboratory, which was destined to make German science celebrated, with a glamour which it did not possess. Actually, it consisted of one room in a deserted barrack which looked like an old stable. Here Liebig taught and investigated for ten years, until a proper laboratory was provided him; and in his laboratory the first teachers of chemistry for all of Germany and for other countries as well were trained. If one were asked to state in a sentence what was the most precious thing which this laboratory contributed to science and to culture, the answer would be 'die Entwickelung des selbständigen Denkens bei der Arbeit' (the development of independent thinking in

[1] Vallery-Radot, R., *The Life of Pasteur*, Garden City, N.Y., Garden City Publishing Co., p. 84.

work). The professorial authority reigned supreme in German instruction at this time, but not so in France, where the lectures were excellent and there was wanting merely the student laboratory. And this voice in Germany was not always conscious of its authority. Ostwald[1] relates an example in which a great scholar unintentionally destroyed the influence of his teaching because he unwittingly impelled the students to find out only that which he had predicted. As a result, he produced, in the course of a long career, hundreds of 'doctors', and hardly a pupil who contributed to knowledge.

Liebig's laboratory was, as a matter of fact, anticipated a year by the physiologist, Purkinje, who fitted up a room in his own house in which to instruct students. This was in Breslau in 1824. Now Purkinje was a physiologist of genius whose great merits have not, perhaps, received the recognition they deserve. There is a further similarity in the careers of these two innovators. Purkinje graduated in medicine in Prague in 1819 and submitted as his thesis a dissertation on subjective visual phenomena, which chanced to bring him the friendship with Goethe, at this time at the zenith of his fame. It is said that it was Goethe's influence which led to Purkinje's appointment as a professor of physiology at Breslau in 1823. There he remained for twenty-seven years, and his influence on the development of physiology in Germany has been aptly compared to that of Ludwig a half-century later, for Purkinje was both the born teacher and investigator, and possessed so modest a temperament that he was content, as was his eminent successor Ludwig, to

[1] Ostwald, Wilhelm, *Grosse Männer*, Leipzig, 1910, p. 167.

sink his own personality in that of the pupils whose published discoveries are those of the master without his name.

Purkinje was not provided with a university laboratory until 1842. But the laboratory in a private house had already become the wedge by means of which experimental science was to be extended in Germany, and in other countries. Buchheim, the pharmacologist and teacher of Schmiedeberg, opened a laboratory in his own house in Dorpat with his private means in 1849. Godlee tells us that after each of Lister's migrations, one room in his house was at once devoted to the purposes of a laboratory. When Ehrlich in 1887, after Frerichs's death and Gerhardt's succession, was deprived of a laboratory, he fitted up a room in his house in which he continued his studies and from which Robert Koch rescued him in 1890. Koch himself carried out his epochal studies on anthrax and on wound infection in his house in Wollstein, the researches which led, through Cohnheim's influence, to appointment to the Imperial Health Department (Kaiserliches Gesundheitsamt) in Berlin in 1880. But for us at this time, the most important home laboratory was that of Ludwig Traube in which were begun those experimental investigations of clinical problems destined to influence the developments taking place in Oxford to-day.

It was natural that laboratories for the fundamental sciences should be developed before those of the clinic were established. Sixty years were to elapse between Liebig's and Purkinje's beginnings and the opening of the investigator-student laboratory in von Ziemssen's clinic in Munich in 1884. In the meantime the modern physiological, pharmacological, pathological, biochemical, and hygienic laboratories were introduced in Germany. The first biochemical laboratory was created for Hoppe-Seyler in Strassburg in 1872, and the first hygienic laboratory for von Pettenkofer in Munich in 1878.

The laboratory which stands nearest the clinic is the pathological, and the first independent one was given Virchow at the Charité in Berlin in 1856. Its origin is historically significant. It was the price paid by the Prussian government for Virchow's return from Würzburg whither he had been banished in 1848 for his too liberal opinions. Its influence on scientific medicine is incalculable. The laboratory contained provision for work in pathological anatomy, experimental pathology, and physiological and pathological chemistry, and it has remained the model for pathological laboratories since constructed all over the world. In it were trained the outstanding pathologists of Germany: to it were attracted pathologists from all other countries. It played a remarkable role in the training of biochemists. Hoppe-Seyler was an assistant here before becoming professor of chemistry at Tübingen and of biochemistry at Strassburg; and Kühne, later professor of physiology, a pupil of Claude Bernard's, and physiological chemist also, the teacher of Cohnheim in Germany and Chittenden in New Haven, had been a chemical assistant of Virchow's. A special feature of Virchow's laboratory was that it emphasized the study not only of diseased structure, but also of disordered function, and employed not only the methods of observation, but also of experiment.

Virchow stands out as the giant of the Berlin school of medicine whose influence on the growth of scientific medicine after the middle of the nineteenth century was paramount. His genius was precocious. At the age of twenty-five, with Reinhardt, he began the publication of the *Archiv* which bears his name and which was comprehensively dedicated to pathological anatomy, pathological physiology, and clinical medicine. The *Archiv* is a great store-house of medical knowledge. Huxley wrote that if all the books in the world except the *Philosophical Transactions of the Royal Society* were destroyed, it is safe to say that the foundations of physical science would remain unshaken, and that the vast intellectual progress of the last two centuries would be largely, though imperfectly, recorded. With the necessary verbal changes, this statement could be applied to Virchow's *Archiv* in relation to pathology and experimental medicine.

The fruitful developments outside the clinic could not remain indefinitely without influence on the hospital. The natural and inevitable result was the establishment of the clinical laboratory, not for diagnosis only, but for the teaching of students and the conduct of research. The germ of this idea may be traced back to such men as John Hughes Bennett, who described leukemia in 1845, and Lionel Smith Beale in Great Britain, and to Frerichs and Traube in Germany, who applied microscopical, chemical, and experimental methods to the investigation of clinical problems of disease. But the first co-operative investigation of a disease ever undertaken was that of Bright at Guy's Hospital in 1842. A complete clinical unit with consulting-room and laboratory was provided. The results were published by Barlow and Reese in 1843 after Bright's retirement.

Although in our day Germany led the advance in scientific medicine, up to the middle of the last century it was still in the grasp of the natural philosophy school. Meanwhile, in France and England, medical science had become objective and even experimental. Laennec had discovered auscultation and had impressed upon diagnosticians the importance of having their inferences confirmed by autopsies. Modern pathological anatomical diagnosis of disease was growing up in Great Britain and France, and a new therapeutics was being taught by such men as Louis, Cruveilhier, Graves, and Abercrombie, while in Germany, Hufeland, the physician of Goethe and Herder, was still 'a star of the first magnitude'.[1] It was the day of Magendie in France; also, because of French influences chiefly, the day of Johannes Müller, anatomist, physiologist, and pathologist, and Schönlein, modern clinician, who were rising in Germany.

Johannes Müller, son of a cobbler at Coblentz, was born in 1801, entered the University of Bonn at the age of eighteen, was made professor there in 1830 at the age of twenty-nine and professor in Berlin at the age of thirty-three. Müller began his medical career as a disciple of the natural philosophers, but under the influence of the physiologist Rudolphi of Berlin, whose successor he was to become, he was led to renounce the system in favour of the natural sciences. Like Haller and John Hunter, he was one of the great all-round medical naturalists, and he became eminent in very diverse biological fields. His greatest contri-

[1] Naunyn, B., *Erinnerungen, Gedanken und Meinungen*, Munich, 1925.

butions to science resided in the men he trained: Schwann, the founder of the cell theory; Henle, the anatomist who formulated precisely in 1840 the germ theory of disease; Traube, the clinician and experimental pathologist; Helmholtz and DuBois Reymond, physiologists; and Virchow, the founder of the cellular pathology.

Schönlein, like Müller, was of simple origin. Born in 1793, the son of a master rope-maker at Bamberg, he also came under the influence of the prevailing natural philosophy, from which he freed himself less completely than did Müller. He never ceased to think of disease as 'an entity'. But at Würzburg, whither he went in 1813, he found exceptional opportunities for medical studies and had as teacher Döllinger, the teacher of von Baer, the embryologist, who had escaped the mystical trend of the time. Schönlein's rise was rapid. In 1824 he became ordinary professor at Würzburg, and established there, as he was later to do in Berlin, a clinic in the new sense, that is a clinic in which auscultation and percussion were practised, and microscopical and chemical examinations carried out, and where the diagnosis was checked at autopsy. He suffered for his liberal political opinions as his pupil Virchow was to do later, was driven from his professorial position and given refuge at Zürich. In Zürich he made the discovery which has made his name familiar: he described the fungus, afterwards named *Achorion schönleinii*, which causes a disease of the scalp. This was in 1839 and just three years after Angelo Bassi had discovered the fungus cause of muscardine, a disease of silkworms. These observations were to affect later the doctrine of the germ origin of disease.

When Schönlein came to Berlin in 1840 medicine was still being taught by lectures in Latin. He introduced lectures in the vernacular, and objective and laboratory methods of teaching. And he became the teacher of Traube and of Virchow, on whom he exerted a profound influence.

The strength of the German school of medicine under Müller and Schönlein lay in the recognition of the natural sciences as the foundation of medicine, and this was the base on which the new school was to rise after the work of those two great men was over. Nowhere else, except in Germany, at that time did the methods of physics, chemistry, physiology, and pathology penetrate into the clinic. Experimental pathology came to life in the clinics, especially in those devoted to internal medicine.[1]

Schönlein was succeeded by the brilliant Frerichs, and later Traube also was to be given a clinic in the Charité. Both men were trained in the natural sciences and thought in terms of these sciences, but they differed in personality and in detailed training. Traube's foundations were laid in physiology chiefly, while Frerichs was not only an accomplished physiologist, but an able chemist and pathologist as well. But what is important for us is that both men were experimentalists, used the laboratory to investigate clinical problems, and brought the knowledge which the laboratory and experiment had yielded into their clinical teaching. Frerichs was a fascinating lecturer. 'Students hung on his lips and his colleagues revered his wonderful precision in diagnosis.'[1] He paid great

[1] Garrison, F. H., *History of Medicine*, Philadelphia, W. B. Saunders & Co., 4th edition, 1929, p. 619.

respect to clinical observation as such, because upon it rested diagnosis, and in his lectures he was a casuist, presenting his arguments skilfully and citing his own experience chiefly, because at that time in German literature there was little good clinical commentary.

The laboratory attached to Frerichs's clinic at the Charité consisted of one small room; even the assistants could scarcely find space for work in it. Frerichs is remembered for his discovery of leucin and tyrosin in the urine of acute yellow atrophy of the liver, his pathological studies of cirrhosis of the liver, his book on Bright's disease and diseases of the liver, and a monograph on diabetes based on a large number of cases with autopsies, published a short time before his death. He was the teacher of Ehrlich, Naunyn, Leyden, von Mering, all of whom have left impress on modern medicine.

Traube had sat under a galaxy of great teachers, including Purkinje, Johannes Müller, Skoda, Rokitansky, and Schönlein. He was the father of experimental pathology in Germany. His predilection was for the methods of physiology, in which he was master. He commanded little chemistry and pathological anatomy, for the latter depending upon his colleague, Virchow. He investigated the pulmonary disorders occasioned by the section of the vagus nerve, the pathology of fevers, the effects of digitalis and other drugs, the relation of cardiac and renal disorders, and introduced the thermometer in his clinic as early as 1850. Virchow says of him in his obituary appreciation that 'many are called and only a few are chosen. Among the chosen was Traube.' He was the clinician endowed with the temperament of the investigator, always searching for explanation (*Erklärung*). He was an enemy of the speculative tendency of the time. His collected papers appeared between 1871 and 1878, and to them he wrote a Foreword which was essentially the introduction to his short-lived *Beiträge zur experimentellen Pathologie und Physiologie*, published in 1846. He advocated the rigid use of the scientific method. 'This consists in adding to passive observation the employment of the experimental method, which in the case of pathology likewise is capable of advancing it in the direction it is seeking—that of becoming an exact science,' and 'in addition to the most exacting observation of the patient at the bedside and at the autopsy, the use of accurate experimentation is the main task of the present pathology.'

Osler spent several months in Berlin in 1873 and recorded his impressions of Virchow, Frerichs, and Traube. He was back in Berlin again and visited the clinics at the Charité in 1884, at which time he wrote of Frerichs, Leyden, and Westphal that 'the wards are clinical laboratories utilized for the scientific study and treatment of disease, and the assistants under the direction of the Professor carry on investigations and aid in the instruction. The advanced position of German medicine and the reputation of the schools as teaching centres are largely fruits of this system.'[1] It was observations such as these which led Osler to state that 'my second ambition has been to build up a great clinic on Teutonic lines here (in America) . . . lines . . . which have placed the scientific medicine of Germany in the forefront of the world'.[2]

[1] Cushing, Harvey, *The Life of Sir William Osler*, Oxford, Clarendon Press, 1925, 1, 225.

[2] Osler, William, *Aequanimitas*, London, H. K. Lewis & Co., 1925, p. 472.

At the time we are considering, before the last decades of the nineteenth century, the professor of medicine was teacher, hospital physician, and consultant, as he generally still is. His laboratory, such as it was, adjoined his clinic and was used by him and his assistants. The medical student received no practical laboratory instruction to speak of. It was in this kind of laboratory that Frerichs and Traube and their assistants laboured.

And it was in such a laboratory attached to Frerichs's clinic that Ehrlich developed his revolutionary studies on the morphology of the blood corpuscles, white and red. To-day in every hospital where modern medicine is practised the methods of Ehrlich are used for diagnosis and research. His skill in chemistry enabled him to devise diagnostic methods for typhoid fever (the diazo reaction) and for the presence of bilirubin (sulpho-diazo-benzol test), and to determine by means of dye-stuffs the oxygen requirements of the different tissues during life.

This is not the occasion to deal with Ehrlich as immunologist and chemotherapeutist. His discoveries in both these fields have assured his fame. It is proper to say, however, that although separated later from the clinic, he continued often to take his ideas from it. He remained always the fundamental type of investigator interested in disease. He evolved a conception of immunity called the side-chain theory, now outmoded, but among its practical fruits are the Wassermann reaction, for which it was responsible, and also, in essence, the perfection of salvarsan, developed on the basis of the conception of relation between chemical constitution and pharmacological action.

Naunyn was assistant to Frerichs for nine years, and after filling professorships in several universities, was called to the chair of medicine in Strassburg in 1888. After the Franco-Prussian war of 1870, Germany established at Strassburg one of its strongest universities. Naunyn continued his interest in the metabolic diseases derived from Frerichs's teaching. His studies of liver function, icterus (jaundice), and diabetes occupied him all his life. His pupil Stadelman investigated the relation of beta-oxybutyric acid to diabetic coma and Naunyn himself coined the term acidosis to describe the pathological condition present in that state. His assistant Minkowski, endowed with rare skill as an experimental surgeon, excised the liver in birds and the pancreas in dogs and discovered that acutely fatal diabetes follows the removal of the latter organ. This was in 1889. Thirty years later Banting, on the basis of the experiment, was to succeed in extracting and purifying the hormone insulin, which has made diabetes a remediable disease.

There has been discussion of the question whether Banting's great discovery could have been made in a laboratory attached to a clinic. My view is that it could have been made in any well-equipped and technically staffed physiological laboratory, irrespective of its location. There is nothing recondite in the methods employed. Banting at the outset was a physician, not an experimentalist. His original personal contributions to the solution of the problem he undertook were his faith and determination. Everything else he could procure from the provisions offered by a modern laboratory.[1] The environment of the clinic would

[1] Banting, F. G., *Edinburgh Med. J.*, 1929, 36, 1.

surely have been sympathetic to him, and the wards would have supplied him with the human patients on whom the action of the insulin had finally to be tested.

That the investigator in the general laboratory of the medical school is influenced by problems of disease can be illustrated by notable instances. Cohnheim, perhaps the most eminent general pathologist of our time, wished to be a clinician, but opportunity for a suitable hospital appointment was denied him. He had studied physiology with Willy Kühne, a pupil of Claude Bernard, and with Ludwig. Failing in his first ambition, he attached himself to Virchow's laboratory, where his unusual talent soon distinguished him. As one studies the problems he chose to investigate one asks oneself how far his change of vocation affected essentially his interest in disease. His methods were those of physiology. His main themes were taken from the clinic. To my teacher, Dr. William H. Welch, he assigned the problem of acute pulmonary edema, clearly taken from the clinic, and his famous demonstration of the infectivity of tuberculosis before the days of Koch by means of inoculation of the anterior chamber of the rabbit's eye, where the tubercles could be seen actually to develop—*inoculo ad oculos*, in Weigert's words—was a clinical-pathological problem.

But the most impressive example of all is that of Virchow himself. He was a contemporary of Frerichs and Traube, and the scientific leader of the Berlin school. Their ages were almost the same: Virchow was born in 1821, Frerichs in 1819, and Traube in 1818. But Virchow was far the ablest and most versatile of the remarkable trio. It is desirable to recall that he was the pupil of Johannes Müller, who led him into the natural sciences, and of Schönlein, who led him into the scientific clinic. He remained true to these remarkable teachers all his long and varied life. Virchow saw almost more clearly than any of his contemporaries that the laboratory and the clinic are united. At the very outset of his career his teacher, Robert Froriep, partly pathologist, partly clinician, assigned him the problem of phlebitis—inflammation of the veins. The theme was not a new one, but it was a major one in medicine. John Hunter had attacked it. Cruveilhier, the leading French pathologist of his time, had said that it dominated all of pathology. To Virchow it yielded a rich variety of results: the first understanding of leukaemia, which Hughes Bennett had described clinically the same year, in 1845; the vindication for the white corpuscles of a place in pathology; the doctrine of embolism and of thrombosis as the primary condition of phlebitis. And ten years later Virchow was to develop the cellular pathology and to revolutionize medical thinking. He excelled also in the conception of the scientific approach to the problems of medicine which he enunciated. In his article in the first number of his *Archiv*, 'Concerning points of view in scientific medicine', he wrote that disease is life under changed conditions, and scientific medicine is the investigation of these conditions and the means of removing them. He maintained that the methods of investigation and the assistance of the other natural sciences must be employed. Progress, he said, can come only by experiment and observation. He reverted to his old master, Johannes Müller, to point the moral of what he had to say: 'There is no school of Müller in the sense of dogmas, for he taught none, but only in the sense of method'; and he reinforced this precept by the statement that 'it is the method which distinguishes the Harveys, the Hallers, the Bells, the Magendies, and the Müllers from their smaller contemporaries. This is the soul of the natural sciences.'

Welch, in his tribute to Virchow on the occasion of the celebration of his seventieth birthday,[1] linked his name with that of John Hunter, whose immediate successor in the history of pathology he really was, in some respects, although his work was begun fifty years after Hunter's death. 'Both men discarded philosophical speculation and went back to nature, to observation, to experiment for facts on which to build their doctrines. Both made use of all the allied sciences at their disposal, of anatomy in the broadest sense, of physiology, in their investigations, but of course much more was available for the later investigator. Both kept constantly in view the problems of practical medicine, together with the broadest interests and direct participation in science. Both recognized pathological physiology as the foundation of scientific medicine and that this is to be constructed not from anatomical investigations alone, but with the aid of physiology, of experiment and of clinical observation. . . . Virchow took up many problems just where Hunter had left them. The time had come when he could build deeper and stronger and broader on the foundations of scientific medicine.' Welch sums up Virchow's principles: 'Observe; experiment; seek the aid of allied sciences, chemistry, physics, general biology; collect by systematic and purposeful investigation, in

[1] Welch, W. H., *Johns Hopkins Univ. Circ.*, 1891, 11, 19.

which the "Fragestellung" (question asked) is correct and clear, a body of facts, and from them deduce general pathological principles and laws.' General pathology, or pathological physiology, rests upon experiment and clinical observation. Its methods are the methods of normal physiology.

This is the background against which the investigator-student laboratory in the clinic arose. Von Ziemssen was a pupil of Virchow's. He was not himself a laboratory worker; his professional distinction was in the field of the literature and history of medicine. His knowledge was encyclopedic; perhaps this was at the time the best preparation for the innovation he was to introduce into the clinic.[1] When the new hospital in Munich was built in 1878 and attached to the University, he had already provided a modern laboratory for the assistants; the later laboratory for both assistants and students was more comprehensive and embraced three divisions—chemical, physical (physiological), and bacteriological—and included a working library and rooms for the examination of patients.

The enterprise was not carried through without opposition. It was opposed on the grounds that it was unnecessary because of duplication of existing laboratories, because it was uneconomical, and because the laboratories already in existence were competent to look after the problems of disease arising in the clinic.

[1] The investigator-student laboratory in Germany is not designed for the teaching of all the medical students. It is not an 'elementary' laboratory of instruction in methods of diagnosis such as have reached so great a development in other countries and notably in America. It is a place in which advanced students and assistants study primarily problems of disease derived from the patients, but it does not exclude the study of more fundamental scientific subjects.

The final objection was that students would be made too scientific. They would be less good practitioners because they would become too much absorbed in and dependent on laboratory methods. But the idea was a sound one and took root. Curschmann introduced a similar laboratory into his clinic in Leipzig in 1892, and presently there were others throughout Germany.

Some of you will recall a delightful essay of Dr. John Brown's on Locke and Sydenham published about 1858. It chances to be a favourite of mine, and I often think of the good Scottish doctor's anxiety over the march of science in his day which was imperilling the art or practice of medicine. 'This distinction between the science and art or craft, as it is often called the cunning of medicine, is one we have already insisted upon and the importance of which we consider very great, in the present condition of this department of knowledge and practice. We are now-a-days in danger of neglecting our art in mastering our science, though medicine in its ultimate resort must always be more of an art than a science.' These sentiments have a strangely familiar and ominous sound even at the present day when there is still head-shaking in high places over the invasion of the medical curriculum by the laboratory.

In America the developments came much later. A beginning in physiology was made by Bowditch, a pupil of Ludwig, at Harvard Medical School in 1871, and in 1876 when the Johns Hopkins University opened its doors, Newell Martin, a pupil of Huxley and Foster, was given a fully equipped laboratory in biology including physiology. When the Johns Hopkins

Hospital opened in 1889, the clinical departments had only small diagnostic laboratories attached to the wards. All the research in clinical medicine and surgery was carried on in the pathological laboratory, an adjunct of the Hospital. But when the Johns Hopkins Medical School was founded in 1893, model laboratories for the teaching of students and for investigation in the preclinical sciences were provided, and in 1896 a students' diagnostic laboratory was added to the medical clinic. Not until 1905 was the Hunterian Laboratory for teaching and research in surgery under Halsted erected, and only in 1906, when Barker became professor of medicine, was an investigator-student laboratory along German lines added to the medical clinic. Ten years earlier, in 1895, the William Pepper Laboratory of Clinical Medicine, attached to the wards of the Hospital of the University of Pennsylvania, had been opened; and this laboratory, the first of its kind in America, was of the investigator-student type similar to von Ziemssen's laboratory established ten years before.

A great change came with the founding of the Rockefeller Institute for Medical Research in 1901 and especially with the opening of the Hospital of the Institute in 1910. The hospital was designed wholly for research in clinical medicine. Laboratories were provided on the same scale as beds for the patients and in proximity to them. The problems were derived from the patients, but the investigation of more fundamental ones relating to disease was encouraged.

There had already been agitation, in which Dr. William H. Welch took the leading part, concerning the inadequacies of instruction and research in the hospital clinics.[1] Forward-looking men had seen that the steady growth of the medical sciences had thrown increasing burdens on the clinical staff. The multiplicity of their duties and the division of their time between hospital and private practice had made their work increasingly onerous. Justice could no longer be done to the hospital and medical school on the one hand, and outside calls on the other. The time had gone by when the physician could be at once a great consultant and a great teacher.

The physiologist Ludwig in the eighties of the last century had foreseen that it was only a matter of time until the pressure of scientific knowledge and the attendant more exact technique of the clinical laboratory would compel a reform in the clinical branches of medical education.[2] He seemed to sense the additional strain which the impending rise of bacteriology was to impose on the clinical departments, a strain now increased by the current rise of virus pathology, so applicable to the immediate study of disease. The hospital of the Rockefeller Institute was not so much an innovation as a demonstration of Ludwig's prescience and Welch's educational propaganda. Thus the two great teachers, Ludwig in Leipzig and Welch in Baltimore, came to the same goal by different routes.[3] That Ludwig should have foreseen so clearly the inevitable reform thirty years before it actually took place is to be explained on the basis of the

[1] Welch, W. H., *J. Am. Med. Assn.*, 1907, 49, 531.

[2] Sabin, F. R., *Franklin Paine Mall*, Baltimore, the Johns Hopkins Press, 1925, p. 254.

[3] Welch, in his introduction to the English translation of Billroth's *Lehrer und Lerner*, published originally in 1876, states that one may discover in it 'adumbrations of the full-time system'. (*The Medical Sciences in the German Universities*, The Macmillan Company, New York, 1924, p. ix.)

circumstances surrounding his remarkable career. He was perhaps the most influential teacher of physiology who ever lived. He had over two hundred pupils of all nationalities, and most of the younger generation of investigators in his science were trained by him. We have two British tributes to him. Lauder Brunton wrote: 'More than to any one else since the time of Harvey do we owe our present knowledge of the circulation to Carl Ludwig. . . . Like the great architects of the Middle Ages, who built the wonderful cathedrals which we all admire, and whose builder's name no man knows, Ludwig has been content to sink his own name in his anxiety for the progress of his work, and in his desire to aid his pupils.' Burdon Sanderson wrote that the students in Ludwig's laboratory 'for the first time in their lives came into personal relation with a man who was utterly free from selfish aims and vain ambitions, who was scrupulously conscientious in all that he said and did, who was what he seemed to be and seemed what he was, and who had no other aim than the advancement of his science'.

But another personality exerted a profound influence on the new developments about to be introduced into clinical teaching and research in America. Mall, the professor of anatomy at the Johns Hopkins Medical School, had been with Ludwig in 1885 at a time when the teacher was expounding his revolutionary ideas. Mall was converted to them, and being himself by temperament a reformer in medicine, urged them in Baltimore.[1] It was the right place: the Johns Hopkins University had made a successful experiment with its

[1] Sabin, F. R., *Franklin Paine Mall*, Baltimore, the Johns Hopkins Press, 1925, p. 254.

Medical School; it was now to make a second experiment, perhaps fundamentally as significant, in relation to the clinic.

By 1911 the University was ready to introduce the university clinic. The General Education Board, one of the Rockefeller philanthropies, proved co-operative, and in 1913 a formal application was made to the Board for the funds necessary to place the three main chairs—medicine, surgery, and pediatrics, to which obstetrics was added later—on the full-time system. The application of the University was prepared by Welch. On 23 October 1913 the General Education Board appropriated the funds needed to put the plan into effect. In the letter announcing the gift, the following citation occurs: 'That, in view of Dr. Welch's great services to the cause of medical education, the fund appropriated be called "The William H. Welch Endowment for Clinical Education and Research".'

'It is inspiring to contemplate', wrote Welch, 'the possibilities of a well supported and practically organized medical and surgical clinic upon a true university basis. It would introduce new opportunities for higher standards of teaching and productive research. It would place before students and the profession higher ideals of the mission of the physician and of his relation to the community. It would advance both the science and art of medicine by training investigators, by making better physicians, and by contributing to useful knowledge.'

The plan was put into practical operation at the Johns Hopkins Medical School and Johns Hopkins Hospital with the beginning of the academic year in the autumn of 1914.

II

WE turn now to a consideration of the organization of the investigator-student laboratory in the clinic. It is self-evident that the clinical professors should be skilled physicians, as their first responsibility is the welfare of the patients in their charge. Then, as the purpose of the laboratory is to advance knowledge, they should be investigators as well. Clinical teaching in the past has not prepared men especially for this second office; it is to be supposed that the clinical units already established and the large Nuffield benefaction will add to the number of men so trained.

The investigator-clinical laboratory, as we shall now call it, will not as a rule be large. As it is not intended for usual diagnostic purposes or for elementary instruction, but as a place where the clinical staff and advanced students are to study problems of disease, the size will be determined by the capacity of the wards or units in which the special patients providing the problems are cared for. The clinical investigators will, as a rule, all have duties in the wards as well as in the laboratories, since the two functions are essentially interrelated.

In what is to follow I shall not be dealing specifically with Oxford. I shall be dealing with the question of organization in a more general way and one related rather to the principles of organization than to local plans adopted to-day and subject to change as experience warrants. Nor will it matter especially whether the examples to be given are taken from the more conventional teaching and investigating institution or from the research institution, since the principle is one in both. In the last analysis, there is no non-teaching scientific institution, whatever its name or theory or purpose. Wherever young men, usually in their twenties, are taken in and put to work under highly trained masters, teaching becomes an inevitable as well as a desirable part of the relationship, and as these men grow in numbers, the teaching function becomes not only a real, but a laborious one.

The teaching is a by-product of the task undertaken and is of concentrated nature. I believe that here in Oxford the highly gifted students devote themselves intensively to one or two subjects and the average students work at many. In an institution in which research is cultivated the young men and women may be compared with the first class; they do not, however, necessarily obtain degrees; they receive something as good, at least those who are really talented—namely, a superior preparation for a career in science which they have themselves selected. If I am not mistaken, the grade of students to be admitted and the character of the training in the clinical sciences which it is intended to give in the new units at the Radcliffe Infirmary belong in this latter category.

From the beginning in 1884 in von Ziemssen's laboratory the subjects for which provision was made included chemistry, physiology, and pathology and bacteriology. This group of subjects, embracing as it does the fundamental branches of medical science, has not changed essentially since; and one or another has been more fully developed according to the dominant interests of the professor in charge of the particular clinic. Of course the kind and complexity of the facilities required have undergone change in the intervening years, but what is important is that the integrity of the clinical laboratory has been jealously guarded. It has never been conceived as a rival of the general medical laboratories, but as a complement to them, devoted to the purposes and profiting by the opportunities of the clinic. Nor has it been admitted that it is less scientific or should be subordinated to the general laboratories, with which it aims to co-operate freely. A bond of union between the two sets of laboratories has come to be recognized as essential to the purposes which are to be served in advancing clinical research. But no apportionment of problems between the general laboratories and those of the clinic has been or ever should be undertaken. Indeed, there should be no division of purpose between the laboratories of the medical school; together they should form one domain. The laboratories of the clinic will take their problems from the patients in the wards, but the pursuit of fundamental problems should not be denied them any more than the investigation of problems of disease should be withheld from the general laboratories. Research is an individual thing, and the natural investigator inside and outside the clinic should be given the fullest play possible for the exercise of his talents. Nothing will be lost and much may be gained from this freedom of action.

It is a great gratification that Lord Nuffield, in making the munificent and wise benefaction for medicine, recognized the need to aid the preclinical as well as the clinical laboratories. The general laboratories must be maintained in high efficiency if the laboratories of the clinic are to prosper; they are the foundations on which the students are to build their competence to become clinical investigators, and without their proper support the objects of the Nuffield trust as a whole cannot be attained.

We have already seen that the general pathologist, in taking his problems from the clinic, may advance the whole broad field of pathology. I wish now to bring before you instances in which the clinical laboratory provided the stimulus and the place in which profound problems in biology of great importance to medicine received their solution.

Just the other day Professor Hans Fischer was awarded the Davy medal by the Royal Society for his chemical work on the porphyrins, substances related to the red colouring matter or the haemoglobin of the blood. This research, which eventually yielded artificial haematin identical with the natural product derived from the haemoglobin, helped to explain the mechanism of bile-pigment formation. Later studies have led to the elucidation of the structure of chlorophyll. The research on this problem was begun in the clinical laboratory of the hospital in Munich under Friedrich Müller. Although the later stages of the investigation were carried out in the laboratory of the technical high school in Munich in which Fischer is professor of chemistry, the clinical relations of the problem were never overlooked.

The story of the unravelling of the chemical nature of the specific types of pneumococci is a comparable one. In its solution, clinician, pathologist, and chemist co-operated in the laboratories of the hospital of the Rockefeller Institute. In 1917 Dochez and Avery described the 'soluble specific substances' given off in the growth of pneumococci in artificial cultures and in the body. These substances, readily detected by immunity tests, are found during life in the blood and in the urine of animals and men infected with pneumococci. When the study was begun in Dr. Cole's laboratory some twenty years ago three specific types of pneumococci were known; now more than thirty distinct immunological types have been described. Avery and Heidelberger discovered that the source of this specificity is a complex sugar—a polysaccharide—which can be obtained in pure crystalline state and which is the basic constituent of the soluble specific substances. The sugars differ among themselves in the same way as do the specific pneumococci with which they correspond immunologically. They come from the capsules of the micro-organisms in which they determine specificity and pathogenicity. In the disease the sugars are injurious not through their direct poisonous action, but because they unite with and render inactive the healing antibodies and because they depress phagocytosis. Not only pneumococci yield specific substances; other pathogenic bacteria do so likewise. And now that the chemistry of the pneumococcus specific substances is known, the way has been opened for the artificial production of them and for the preparation of artificial antigens capable of yielding antisera active against pneumococcus infections.[1]

The two examples just given have an immediate bearing on the organization of the clinical laboratory because they show the importance of the biochemist to it. They are instructive for another reason. They show that the biochemist should be primarily a highly

[1] Goebel, W. F., *J. Exp. Med.*, 1938, 68, 469.

trained chemist. He may have a medical degree also, as Hans Fischer has; but the paramount consideration is not that, but his competency as a technical and gifted chemist.

This consideration reminds me of an apposite personal experience which I would like to share with you. I came to Europe soon after the opening of the hospital of the Rockefeller Institute in 1910, in search of a biochemist. I consulted the leading chemists of the day. I was unsuccessful in obtaining a suitable candidate. We decided to take a gifted young chemist and place him in the hospital. The choice was Van Slyke, then associated with Dr. Levene in the biochemical laboratory of the Institute. Van Slyke's original training was in organic chemistry, but he early showed a special talent for physical chemistry. Had he developed outside the hospital his interests would have been directed to the application of physico-chemical methods to structural chemistry. In the clinical laboratory he was confronted with the problem of acidosis in diabetes and he concentrated his attention on the development of methods of blood analysis, which resulted in his discoveries in acid-base regulation in health and in disease. As time went on other contributions to quantitative clinical chemistry came from his laboratory, the responses to the conditions arising within the clinic and the medical atmosphere surrounding him. It is not without interest that it was while Heidelberger was working in Van Slyke's laboratory that he became interested in the pneumococcus problem being studied in an adjacent laboratory. In this way his co-operation with Avery, so fruitful for bacteriology as well as for medicine, came about.

The kind of organization indicated by these examples inevitably introduces into the hospital staff men without initial medical training or clinical experience. In the choice of chemist and bacteriologist emphasis is placed on technical training and individual talent rather than on preparation in medicine. So far as clinical needs are concerned, they are provided for by others on the medical staff, since chemist and bacteriologist work in close connexion with the clinicians. Moreover, experience shows that these non-clinical laboratory men learn to think clinically and to take problems directly from the patients, and in time, as they are permanent members of the hospital staff, they may come even to surpass their medical associates in this respect.

In a way, the use of the pure chemist in the manner I have indicated is perhaps not so much a matter of expediency as of necessity, dependent on the developments going on in biochemistry itself. Sir Frederick Hopkins has recently said that the entrance of eminent and enlightened organic chemists into the biochemical field is the happiest augury for medicine. Physiology and pathology are relying more and more on chemical interpretations of the phenomena with which they deal. The field for the organic chemist, therefore, is enlarging and he is becoming indispensable to the medical, and so to the clinical, laboratory.

There is general agreement that the laboratories of the clinic should be located in the hospital if possible, and in any event in proximity to the wards. The hospital staff—assistants and students—should have ready access to them, both by day and by night, and while there, should be within immediate call for emergencies. Moreover the clinics with their associated laboratories should be near, very near if possible, to the general school laboratories. A spirit of easy and free co-operation between them should be encouraged. This advantage was early recognized in Germany; it has been kept in mind in designing the new university clinics in America. At the Rockefeller Institute, covered corridors, heated in winter, connect hospital and general laboratories, and passage from one to the other is made so easy that the effect is of one common building for all.

Science thrives best in an atmosphere of research, or, as has been said, where research is in the air. Now, the particular kind of research which the air of the hospital fosters is clinical research; therefore it is desirable that those who guide and take part in it should work in the hospital atmosphere. This atmosphere is formed by the men who toil in it. Hence the men who create, deepen, freshen, and make it more fruitful should not be withdrawn from the hospital and placed in the general laboratories. All other considerations, when possible, should give way to this essential condition. The clinical atmosphere cannot be introduced into the general laboratory. The two kinds of laboratory—clinical and general—by co-operating can give to the medical school that stimulating and sympathetic quality which is the best insurance of the life and productivity of the school.

Medicine is a composite science. It is built on a foundation of biology, chemistry, and physics, and it is not restricted to human ills. Not only man suffers from disease and presents problems in pathology; animals lower in the biological scale also suffer from disease; we recognize this fact in veterinary medicine. But veterinary medicine has economic boundaries, and disease has not, so that the animal diseases embrace the entire animal kingdom.

Plants also have diseases, which we recognize by setting up laboratories for plant pathology. That branch of pathology also has been limited by economic considerations. As a matter of fact, medicine, properly speaking, is a comparative science and includes all orders of living things: man, the lower animals, plants, from the unicellular to the multicellular organisms, from the noblest and the highest to the humblest and the lowest individuals.

It is only through unrestricted research in comparative medicine that the problems of disease can ultimately be solved. It is an old experience to transfer human disease to a lower animal in which it may be investigated more completely. This artificial, although often profitable, process can be extended by the study of animal diseases as they occur in nature in the same way as human diseases occur, and likewise with the diseases of plants.

It became possible to set up laboratories at the Rockefeller Institute for the investigation of the diseases of animals and the diseases of plants. Although the two new divisions adjoined each other, being located not far from New York in suitable space found available near Princeton, New Jersey, where a university atmosphere existed, each laboratory was made complete and independent of the other. There was cooperation, of course; but the staff of each worked on problems in the atmosphere created by the subject—the diseases of animals on the one hand, and the diseases of plants on the other. In a sense the work was carried on in a clinical atmosphere—that of sick animals and, if you please, of sick plants—so that again the organization was on a functional basis; progress made in the investigation of animal disease helped in the study of problems of plant disease and both helped in the study of human diseases in the laboratories and hospitals in New York.

Disease can be more completely studied in the lower forms of life than in man. In man many aspects of disease must be studied through symptoms and by inference as to their meaning. Now in the lower forms of life disease can be terminated at any desirable time and an objective and searching study made of the pathological conditions existing. Moreover, in the experiments, animal disease is not transferred and reproduced or imitated in a foreign species; it is reproduced in the same species and under accurately controlled conditions; also, diseases are investigated as they occur naturally in these lower forms just as we say diseases arise spontaneously in man.

Progress in any field of pathology often illuminates work in other fields of that science. Just as comparative anatomy enriched human anatomy, so the study of comparative pathology is enlarging and clarifying the study of human medicine. These statements can be illustrated by many examples. I shall confine myself to two instances, both of recent occurrence. The fatal disease of horses, equine encephalomyelitis, has long prevailed in America, where two varieties are recognized according to their geographic distribution—an eastern and a western variety. In symptoms and in pathological effects the two varieties are indistinguishable. Recently, both varieties of the disease have been shown to be caused by viruses which in turn are differentiable immunologically one from the other.

We have long known that certain diseases native in the lower animals are sometimes communicated to man. Anthrax and rabies are examples of such diseases. Very recently it has been found that the virus of equine encephalomyelitis may pass to human beings and cause in them a fatal inflammation of the brain and spinal cord. These organs contain the virus, which may again be transferred to horses, and the virus retains in man the specificity—eastern or western—which it possessed in the horses. In other words, discoveries made in connexion with equine encephalomyelitis have served to explain what would otherwise have been a puzzling, fatal disease in man and have given indications how this disease may be averted.[1] In the horse the virus gains access to the blood through the bites of particular mosquitoes; it also is infectious by instillation into the nose. Knowledge of these facts will permit greater protection of persons who are exposed to the disease in horses.

When von Ziemssen organized his investigator-clinical laboratory in 1884, he set one division aside for bacteriology, which had, under Koch's influence, just come to have such important implications for the diagnosis and perhaps the prevention and treatment of disease. The faith shown was abundantly justified in the next years, and bacteriology became the indispensable adjunct of the medical clinic. To-day the

[1] Wesselhoeft, C., Smith, E. C., and Branch, C. F., *J. Am. Med. Assn.*, 1938, **111**, 1735.

viruses rival the bacteria as recognizable causes of disease, and their study is becoming indispensable to the clinic. Stanley's recent discovery of the crystalline character of the tobacco mosaic virus and the progress made in unravelling the nature of other viruses have an interest for the clinical as well as for the general laboratory. The viruses may be said to 'interest the pathologist since they cause disease, and the bacteriologist because of their small size and because they possess certain properties that have been regarded as belonging to organisms. The chemist is attracted to them because, although they have many of the properties of molecules, they possess in addition properties that have not hitherto been ascribed to molecules. The physicist is interested in them because of their properties as macromolecules and because some virus proteins show that interesting layering phenomenon that has been called a new property of matter. They are of interest to the biologist because they possess properties that have been regarded as characteristic of both living and non-living things. The geneticist is interested in them because they undergo a phenomenon similar to mutation and thus may possibly permit a study of the nature of mutation from a new viewpoint. Lastly, they interest the philosopher because they permit him to enter with renewed vigour upon a discussion of that age-old question of "What is life?"'[1]

[1] Stanley, W. M., *Isolation and Properties of Tobacco Mosaic and Other Virus Proteins*, Harvey Lectures, 1937–8, 33, 170.